Hypocalcemic seizure and related factors after neonatal period; A single-center, retrospective study

Masoume Bitaraf[1], Mohsen Pourazizi[2,*], Behrouz Bavarian[3], Aria Sotoudei[4], Ali Rashidy-Pour[5], Ali Rabbani[4], Fereidoon Mostafavi[4]

[1]Department of Internal Medicine. Tehran University of Medical Sciences, Tehran, Iran
[2]Students' Research Committee, Semnan University of Medical Sciences, Semnan, Iran
[3]Department of Paediatric, Children's Medical Centre, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Pediatric Endocrinology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[5]Research Center and Department of Physiology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.

*Corresponding Author: email address: m.pourazizi@yahoo.com (M. Pourazizi)

ABSTRACT

Seizures are the most common disorder of the central nervous system in childhood and constitute a significant number of admissions to the pediatric emergency departments. The aim of this study is evaluate the etiology of hypocalcemic seizures in pediatrics. A single-center, hospital based descriptive study was done in the academic referral center for hypocalcemic seizure of Tehran University of Medical Sciences, Iran. Data was evaluated based on the medical records of each patient. Case files of these children's were analyzed for age at presentation, sex, weight, clinical features, biochemical parameters (serum calcium, magnesium, phosphorus and alkaline phosphatase) ,type of seizure, history of previous seizure and history of drug intake**.** A total 38 children with hypocalcemic seizure, consisting of 19 boys and 19 girls, with ages ranging from one month to 14 years, were enrolled in this study. The most common patterns of seizures were generalized seizures (83.8%). the mean levels of serum alkaline phosphatase was significantly greater in patients under the age of 2 years (1234 ± 541.03) rather above than 7 years of age (922.75 ± 147.45) (p = .021). Rickets was the commonest cause of seizures rickets were diagnosis in 80.8% subjects under 2 years of age, whereas none of those over 7 years old had not rickets , these results were statistically significant (p = .015). Current observational study indicates that rickets could be a major cause of hypocalcemic convulsion in infants and children. Screening children presenting with hypocalcemic convulsions for rickets and/or other cause of hypocalcemia can help in early diagnosis and institution of specific therapy.

Key words Seizures; Pediatrics; hypocalcemia; Rickets.

INTRODUCTION

Seizures are the most common pediatric neurologic disorder, with 4% to 10% of children suffering at least one seizure in the first 16 years of life[1]. The incidence is highest in children younger than 3 years of age, with a decreasing frequency in older children[2]. Etiology of seizures were classified broadly as idiopathic (due to an epileptic syndrome), cryptogenic (due to a neurological disorder) and secondarily provoked by other causes such as fever, infections, metabolic, and electrolyte imbalance [3]. When a child presents with a seizure, every effort should be made to determine the cause. It is imperative to differentiate between a seizure and other non-epileptic conditions that may mimic seizure activity such a hypocalcemia [4].

There are multiple causes of hypocalcemia in children; thus, diagnosis must follow a systematic approach. The differential diagnosis of hypocalcemia in children includes Vitamin D Deficiency (VDD), hypoparathyroidism, pseudohypoparathyroidism , pseudo-pseudohypoparathyroidism ,hypomagnesemia, malabsorption, hyperphosphatemia and renal and hepatic failure, among others[5, 6]. Reasons for VDD and subsequent hypocalcemia include inadequate dietary intake of calcium and vitamin D, malabsorption, inadequate exposure to sunlight, renal and liver disease and medications[7]. The classical manifestation of VDD is rickets, but in some pediatrics, severe hypocalcemia and seizures may present [8]. Some children with hypocalcemia will be found to have rickets, but not all children with rickets

will be hypocalcemic [6]. Hypoparathyroidism, a major cause of pediatric hypocalcemia, is caused by impaired secretion or production of parathyroid hormone (PTH), a defect in the calcium sensing receptor that regulates PTH secretion, or end-organ resistance to PTH [6]. Hypocalcemia in children may be asymptomatic or there may be a wide range of signs and symptoms. Because very young patients cannot accurately verbalize symptoms, they are more likely to present with signs such as weakness, feeding problems, facial spasms, jitteriness or seizures[9].

There is limited data on pediatric hypocalcemia and pediatrics hypocalcemic convulsions. So the aim of this study is evaluate the etiology of hypocalcemic seizures and related factor in pediatrics older than 1 month.

MATERIALS AND METHODS

A single-center, hospital based descriptive study was done in the academic referral center for hypocalcemic seizure of Tehran University of Medical Sciences which is the main center for treatment of pediatrics seizure with metabolic etiologies in Tehran, Iran.

The medical records all hospitalized children presenting with history of convulsions were worked out for the cause of convulsion and those children who were found to have hypocalcemic convulsion dating between April 2008 to April 2012 were reviewed to evaluation the main etiology hypocalcemic seizure, level of calcium and related factors in the convulsion after neonatal period in the childhood. All patients with hypocalcemic seizures were included. Excluded from the study were neonates. Data was evaluated based on the medical records of each patient. Case files of these children were analyzed for age at presentation, sex, weight, clinical features, biochemical features including total Serum calcium (mg/dL), Serum magnesium (mg/dL), Serum phosphorus (mg/dL) and Alkaline phosphatase (IU/L), type of seizure, history of previous seizure and history of drug intake. The diagnosis of hypocalcemic seizure was made on the bases of clinical and biochemical features. The diagnosis of rickets was based on clinical features, biochemical parameters (Serum calcium, phosphorus and alkaline phosphatase) . Hypocalcemia was diagnosed when serum calcium < 8.4mg/dL, Serum magnesium, the normal range was 1.5-2.7 mg/dL. Hyperphosphatemia was diagnosed when serum inorganic phosphate was >7 mg/dL. The upper limit of normal for Alkaline phosphatase in infants was 1076 IU/L.

Patients were classified into three groups, <2 years, 2-7 years and >7, also rickets group and non-rickets group of hypocalcemic convulsion group. The statistical analysis of the study was conducted using SPSS 16 and differences with $P< 0.05$ were considered significant.

RESULTS

38 children with hypocalcemic seizure, consisting of 19 boys and 19 girls, with ages ranging from one month to 14 years were enrolled in this study. All the 38 children presented with history of convulsions. In our study, there was no case of hypocalcemic seizure between ages 2-7 years old. The most common patterns of seizures were generalized seizures (83.8%) (Table 1).

Table 1. Demographics and basic characteristics data

Characteristics		Frequency	Percent
Sex	Male	19	50
	Female	19	50
Age	1m- 2 y	34	89.5
	2 – 7 y	0	0
	7-14 y	4	10.5
Weight	Under Weight	2	5.4
	Normal	24	64.9
	Over weight	11	29.7
Seizure type	Generalized	31	83.8
	Multi focal	4	10.8
	Focal	2	5.4
Drug History	Yes	7	18.9
	No	30	81.1

18.9% of pediatrics had positive drug history for hypocalcemia .In children have probably drug-induced hypocalcemic seizures, the most groups of implicated drugs was antiepileptic drug (e.g. phenytoin and phenobarbital). The patient had mean serum calcium concentrations 6.32 mg/mL (Range: 4.2-8.4 mg/mL). Their mean serum Alkaline phosphatase and inorganic phosphate concentrations were 1197.29 IU/L and 5.55 mg/mL respectively. Using Independent Sample Test, there were no significant difference between male and female patients in mean serum calcium ($p =0.938$), magnesium ($p = 0.845$), phosphorus ($p = 0.721$) and alkaline phosphatase ($p =0 .772$) (Table 2).

Table 2. Biochemical parameters in male and female patients.

		N	Minimum	Maximum	Mean	Std. Deviation	p-value
Serum Ca (mg/dl)	Male	19	4.2	8.4	6.311	1.2613	.938
	Female	18	4.3	8.3	6.339	.9121	
Serum Mg (mg/dl)	Male	12	1.0	2.1	1.683	.3738	.845
	Female	13	0.7	2.1	1.654	.3733	
Serum P (mg/dl)	Male	19	2.6	11.4	5.679	2.3574	.721
	Female	17	2.0	8.7	5.424	1.8192	
Serum Alkph (IU/L)	Male	18	190.0	2400.0	1172	547.6694	.772
	Female	16	386.0	2294.0	1225	501.5313	

Table 3. Biochemical parameters analysis according age of patients.

		N	Minimum	Maximum	Mean	Std. Deviation	p-value
Serum Ca (mg/dl)	<2 y	33	4.2	8.4	6.373	1.1364	.199
	>7 y	4	5.5	6.6	5.925	.4992	
Serum Mg (mg/dl)	<2 y	22	.7	2.1	1.645	.3826	.166
	>7 y	3	1.7	2.0	1.833	.1528	
Serum P (mg/dl)	<2 y	32	2.0	11.4	5.484	2.1472	.520
	>7 y	4	4.3	8.3	6.150	1.7388	
Serum Alkph (IU/L)	<2 y	30	190.0	2400.0	1234	541.0306	.021
	>7 y	4	796.0	1113.0	922.750	147.4548	

Table 4. Relation of sex, age, weight and seizure type with Rickets.

Variable		Rickets		p-value
		No	Yes	
Sex	Male	2 (14.3%)	12 (85.7%)	.215
	Female	6 (40%)	9 (60%)	
Age	<2 year	5 (19.2%)	21 (80.8%)	.015 *****
	>7 year	3 (100%)	0 (0%)	
Weight	Normal	4 (21.1%)	15 (78.9%)	.390
	Under or over	4 (40%)	6 (60%)	
Seizure type	Gneralized	6 (24%)	19 (76%)	.300
	Non generalized	2 (50%)	2 (50%)	

Using Independent Sample Test, there were no significant difference between patients under the age of 2 years and above the age of 7 years in the mean serum calcium (p = 0.199), magnesium (p = 0.166) and phosphorus (p = 0.520) (Table 3). While the mean levels of serum alkaline phosphatase was significantly greater in patients under the age of 2 years (1234 ± 541.03) rather above than 7 years of age (922.75 ± 147.45) (p = .021) (Table 3). Rickets was the commonest cause of seizures as 72.4% followed by hyperparathyroidism 17.2%, drug induced 6.9, and hyperphosphatemia 3.4%. From 21patients with rickets, 18 patients had nutritional rickets due to vitamin D deficiency and 3 patients had Vitamin D-resistant rickets. Using Fisher's Exact Test, there were not significantly different in development of rickets between the sexes (p = 0.215), weight (p = 0.390) and type of seizures (p = 0.300). Rickets were diagnosis in 80.8% subjects under 2 years of age, whereas none of those over 7 years old had had not rickets , these results were statistically significant (p = 0.015) (Table 4). No significant correlation was noted between level of calcium and phosphor in develop of rickets (p >0.05). But elevated serum Alkaline phosphatase was observed in a significantly higher in the rickets group (1374.61± 552.67) as compared to another group (797.66±205.96) (p =0.02). Among 24 patients with available Electrocardiogram(ECG) records, 41.7% of them had Long Q-Tc .There was no significant correlation between level serum of calcium and Q-Tc interval (p=0.502). No significant correlation was noted between level serum of magnesium and Q-Tc interval (p = 0.305).

DISCUSSION

We report a large population of pediatrics with hypocalcemic convulsion and nutritional rickets in the pediatrics, after neonatal period. In our study, rickets was the most common cause of hypocalcemic convulsion and the most types of rickets was nutritional type due to vitamin D deficiency (VDD). The most frequency of rickets was in the range of 1 month to 2 years

old. Although the classical manifestation of VDD is skeletal manifestations of rickets in childhood, but severe VDD in pediatrics can also present with hypocalcemia and hypocalcemic seizures[10, 11], but suspecting rickets in children presenting with seizures, and other uncommon features is much more difficult[12].In our study the major etiology of hypocalcemic convulsions was VDD due to lack of poor dietary intake and poor exposure to sunlight. VDD and/or nutritional rickets remain prevalent in developing regions of the world[13].

Hypocalcemic seizures are a rare manifestation of rickets; there have been few published data on this issue in recent times. Ahmed et al. have reported 65 infants who presented with hypocalcemic seizures were subsequently found to have rickets[14].Pedrosa et al. reported 4 cases of VDD rickets in Lisbon, Portugal, presenting with variable presentation of severe hypocalcemia secondary to nutritional VDD include: A four-month old girl with several spasms; An eight-day old boy with generalized tonic-clonic seizure; A 9 months old boy with tetany and, a 4 months old boy with cardiogenic shock[8].

Similarly, Balasubramanian, et al. have reported that all 13 exclusively breast-fed infants with hypocalcemic seizures had low serum 25(OH) D [15]. Few other sporadic cases with these hypocalcemic convulsions due to VDD were reported [16, 17].

Nutritional rickets in adolescents has also been reported in Asians and North Africans living in developed countries with a colder climate due to poor exposure to sunlight[18].The cases highlight the importance of child vitamin D supplementation from birth and throughout childhood to prevention the VDD induced hypocalcemia and convulsions.

Our results shows the highest prevalence of hypocalcemic seizure was observed among children aged less than 2 years old. Infants are a vulnerable population for development of VDD because of their high rate of skeletal growth [14, 15, 19].

In our study, there is no case of hypocalcemic seizure between ages 2-7 years old, probably symptomatic hypocalcemia correlates with the periods of rapid growth. Thus the growth rate is an important factor in determining the mode of age of presentation of hypocalcemic convulsion and also symptomatic hypocalcemia can be attributable to the increased metabolic demands of rapid growth during [18, 20]. Additionally, all pre-pubertal children of Middle Eastern descent appear to have increased risk of hypocalcemia because of inefficient formation of vitamin D precursors in pigmented skin[21]. Also in a study of Ladhani et al, All children who presented with symptomatic hypocalcemia were aged either <3 or >10 years [22]. Our results shows, there were no significant differences between boys and girls with regard to the calcium levels. Similarly, Ladhani et al. in a retrospective review of 29/65 pediatrics whom had hypocalcemic symptoms reported there was no difference in sex for the two modes of presentation[22].

Significantly higher elevated serum Alkaline phosphatase in the rickets group as compared to other groups, consistent with the significantly higher. In these children, a lower metabolic demand for calcium would result in a more chronic course of disease, poor mineralization of new bone and increasing osteomalacia[22]. In our study, 18.9% of pediatrics had positive drug history for hypocalcemia, that the most groups of implicated drugs were antiepileptic drug (AED) (e.g. phenytoin, phenobarbital). The effects of AEDs on bone mineral density probably increase the risk for seizures. Preventive measures include optimal supplementation with calcium and vitamin D is necessary for Prevention of hypocalcemic convulsions[23].

The possible pathogenesis of AED-associated hypocalcemic convulsions is likely to be multifactorial, due to factors including impaired in bone mineral density, impaired bone quality (due to osteoporosis and/or osteomalacia and AED-induced hypocalcemia) and impair metabolism of vitamin D (due to drug associated liver dysfunction and enzyme-inducing resulting in failure to 25 hydroxylate vitamin D)[23-25]. Type, dosage and duration of AEDs treatment determine the exact picture of the osteopathy,regardless of whether or not they are enzyme-inducing. Among the enzyme-inducing drugs, especially phenytoin, have been investigated for their influence on vitamin D metabolism [24]. Thus systematic control of the state of bones, calcium and vitamin D status in all patients on long-term treatment with AEDs is nowadays recommended [24].

CONCLUSION

We conclude that nutritional rickets in the pediatrics was the most common cause of hypocalcemic convulsion, after neonatal period , thus a conscious attempt to look for the clinical features of rickets, and a systematic workup, especially in the developing world is very helpful in the early diagnosis , treatment and prevention the serious health effects such as pediatrics hypocalcemic seizure .

REFERENCES

1.McAbee GN, Wark JE. A practical approach to uncomplicated seizures in children. Am Fam Physician 2000; 62: 1109-16.
2.Vining EP. Pediatric seizures. Emerg Med Clin North Am 1994; 12: 973-88.
3.Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989; 30: 389-99.
4.Friedman MJ, Sharieff GQ. Seizures in children. Pediatric Clinics of North America 2006; 53: 257-77.
5.Guise TA, Mundy GR. Clinical review 69: Evaluation of hypocalcemia in children and adults. J Clin Endocrinol Metab 1995; 80: 1473-8.
6.Singh J, Moghal N, Pearce SH, Cheetham T. The investigation of hypocalcaemia and rickets. Arch Dis Child 2003; 88: 403-7.
7.Cashman KD. Vitamin D in childhood and adolescence. Postgrad Med J 2007; 83: 230-5.
8.Pedrosa C, Ferraria N, Limbert C, Lopes L. Hypovitaminosis D and severe hypocalcaemia: the rebirth of an old disease. BMJ Case Rep 2013; 2013.
9.Dawrant J, Pacaud D. Pediatric hypocalcemia: making the diagnosis. Canadian Medical Association Journal 2007; 177: 1494-7.
10.Teaema FH, Al Ansari K. Nineteen cases of symptomatic neonatal hypocalcemia secondary to vitamin D deficiency: a 2-year study. J Trop Pediatr 2010; 56: 108-10.
11.Salama MM, El-Sakka AS. Hypocalcemic seizures in breastfed infants with rickets secondary to severe maternal vitamin D deficiency. Pak J Biol Sci 2010; 13: 437-42.
12.Karunakara B, Sharanabasavesh M, Maiya P, Mallikarjuna H. Convulsions as primary manifestation of nutritional rickets. Al Ameen Journal of Medical Sciences 2013; 6.
13.Hatun S, Ozkan B, Orbak Z, Doneray H, Cizmecioglu F, Toprak D, Calikoglu AS. Vitamin D deficiency in early infancy. J Nutr 2005; 135: 279-82.
14.Ahmed I, Atiq M, Iqbal J, Khurshid M, Whittaker P. Vitamin D deficiency rickets in breast-fed infants presenting with hypocalcaemic seizures. Acta Paediatr 1995; 84: 941-2.
15.Balasubramanian S, Shivbalan S, Kumar PS. Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants. Indian Pediatr 2006; 43: 247-51.
16.Hoecker CC, Kanegaye JT. First place winner. Recurrent febrile seizures: an unusual presentation of nutritional rickets. J Emerg Med 2002; 23: 367-70.
17.Bellazzini MA, Howes DS. Pediatric hypocalcemic seizures: a case of rickets. J Emerg Med 2005; 28: 161-4.
18.Moncrieff M, Lunt H, Arthur L. Nutritional rickets at puberty. Arch Dis Child 1973; 48: 221-4.
19.Chopra N. Study of etiology of seizures in young infants with specific reference to hypocalcemia. MD Thesis 2004.
20.Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976; 51: 170-9.
21.Primary vitamin D deficiency in children. Drug Ther Bull 2006; 44: 12-6.
22.Ladhani S, Srinivasan L, Buchanan C, Allgrove J. Presentation of vitamin D deficiency. Arch Dis Child 2004; 89: 781-4.
23.Mattson RH, Gidal BE. Fractures, epilepsy, and antiepileptic drugs. Epilepsy Behav 2004; 5 Suppl 2: S36-40.
24.Bartl R. [Antiepileptic drug-induced osteopathy. Subtypes, pathogenesis, prevention, early diagnosis and treatment]. Dtsch Med Wochenschr 2007; 132: 1475-9.
25.Andress DL, Ozuna J, Tirschwell D, Grande L, Johnson M, Jacobson AF, Spain W. Antiepileptic drug-induced bone loss in young male patients who have seizures. Arch Neurol 2002; 59: 781-6.